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(54) Vehicles for oral adminstration of pharmaceutically active acide labile substances.

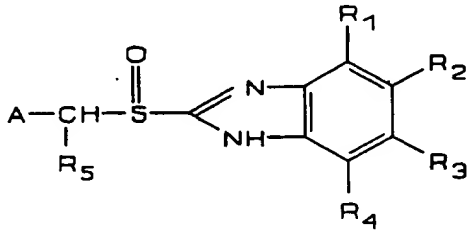
(57) Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances prone to discolouration, containing the acid labile substance where the administration vehicle comprises a core containing said substance together with an alkaline reacting compound or an alkaline salt of said substance optionally mixed with an alkaline reacting compound, adopting the form either of a number of small beads optionally forming a tablet or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

EP 0 565 210 A2

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



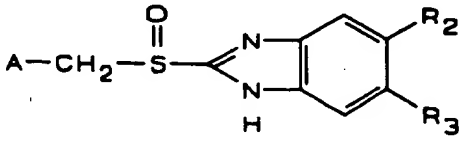
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4, are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

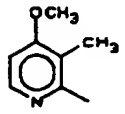
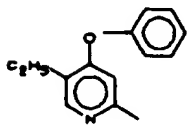
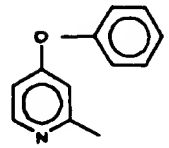
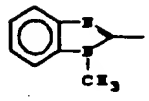
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2	R^3	Half-life (minutes for the transformation to the active moiety at pH=2	at pH=7
1.	5-$COOCH_3$;6-CH_3			11	150
2.	5-CH_3;H			5.4	1700
3.	5-CF_3;H			1.9	122

Cont.

Compound No	A	R^2 R^3	Half-life (minutes for the transformation to the active moiety at pH=2	at pH=7
4.	$5\text{-}CF_3;H$		2.0	8.8
				
5.	$5\text{-}OCH_3;H$		3.7	1620
				
6.	$5\text{-}OCH_3;H$		4.0	3900
				
7.	$5\text{-}C_2H_5;H$		33	not determined
				

Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic

compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

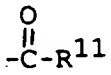
The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3, and R^4, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

alkyl or halogen and R^5 is H or lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acide labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient

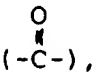
together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

R^1, R^2, R^3 and R^4, which are the same or different and especially

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) -CN
(d) -CHO
(e) $-CF_3$
(f)



(g) $-O-C-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(l) -alkylthio containing 1-6 carbon atoms
(m) $-NO_2$
(n) -akylsulfinyl containing 1-6 carbon atoms
(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 subsituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of theses substituents together form one or two oxo groups



whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same of different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxyalkoxy containing 1-4 carbon atoms
(c) alkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is
(a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is -O- or

;

n is 0 or 1;

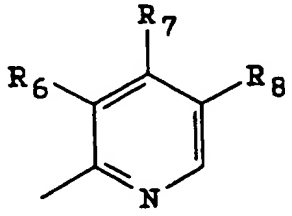
B is

(a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkynylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c)

(d)

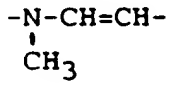
wherein
R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;
m is 0 or 1;
r is 0 or 1;
Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;
R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(d) aryl containing up to 10 carbon atoms;
R^5 is H, CH_3 or C_2H_5;
A is especially a pyridyl group in which R^6 and R^8 are the same or different, are
(a) H or
(b) alkyl containing 1-6 carbon atoms;



R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(f) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$
$-O-(CH_2)_p-$
$-S-(CH_2)_v-$
$-CH_2(CH_2)_p-$
$-O-CH=CH-$
$-NH-CH=CH-$



wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH = 7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less that pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3.4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3 \cdot 6MgO \cdot CO_2 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O)$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Röhm Pharma), or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253 g
	Lactose anhydrous	167 g
	Hydroxypropyl cellulose	25 g
II	Compound 1, Table 1	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5g
	Sodium dihydrogen phosphate	0.1g
	Distilled water	125 g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500 g
III	Hydroxypropyl methyl-cellulose	20 g
	Distilled water	400 g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table 1.

Uncoated pellets

I	Compound 2, Table 1 sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g
	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
V	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
TOTAL	**160 mg**

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [$Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$]	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

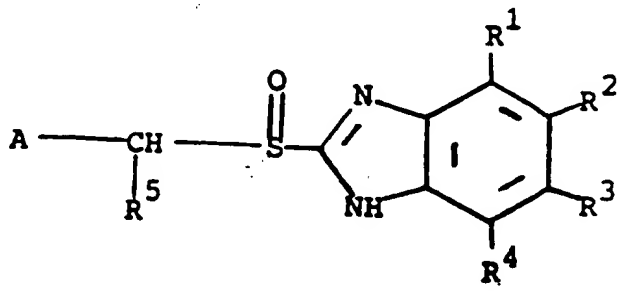
Enteric coating layer

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

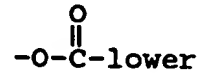
Claims

1. Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances, prone to discolouration, of the general formula



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,



alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl]-sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylamino-benzyl)-sulfinyl]-benzimidazole as

the active ingredient characterized in that the administration vehicle comprises a core containing the acid labile, active substance, stable to discolouration, together with an alkaline reacting compound or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, either in the form of a number of small beads optionally forming a tablet, or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, a polymeric, water soluble, film-forming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

2. Improvements according to claim 1, wherein the subcoating of the core containing the active substance comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.

3. Improvements according to claim 1 wherein the applied subcoating comprises two or more sub-layers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO.\ CO_2.12H_2O$ or $MgO.Al_2O_3.\ 2SiO_2.nH_2O$, wherein n not is an integer and less than two.

4. Improvements according to claim 1, wherein the alkaline core comprising the acid labile compound contains a pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

5. Improvements according to claim 4 wherein the alkaline compound which the acid labile compound is mixed with comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.\ 12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

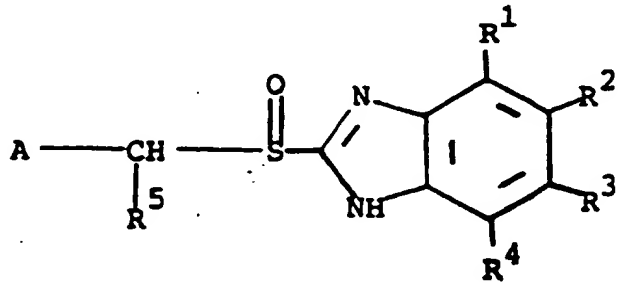
6. Improvements according to claim 1, wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. Improvements according to claim 6 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an otherwise alkaline compound.

8. Improvements according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

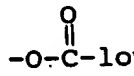
9. Improvements according to claim 1 wherein the dosage form containing the administration vehicle with the acid labile compound has a water content which does not exceed 1.5% by weight.

10. Process for the preparation of vehicles for oral administration of pharmaceutically active acid labile substances, stable to discolouration of the general formula



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,



alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole as the active ingredient characterized in that the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, either in the form of a number of small beads optionally forming a tablet, or a tablet as such are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

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(54) Vehicles for oral adminstration of pharmaceutically active acide labile substances.

(57) Improvements in the vehicles for oral administration of pharmaceutically active acid labile substances prone to discolouration, containing the acid labile substance where the administration vehicle comprises a core containing said substance together with an alkaline reacting compound or an alkaline salt of said substance optionally mixed with an alkaline reacting compound, adopting the form either of a number of small beads optionally forming a tablet or a tablet as such and comprising a coating made out of one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an enteric outer coating layer.

EP 0 565 210 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 20 1612

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 173 664 (AKTIEBOLAGET HÄSSLE) * page 2, line 1 - page 3, line 26 * * page 21, line 26 - page 22, line 8 * * page 27, line 1 - line 20 * * page 37, line 19 - page 38, line 12 *	1,2,4-10	A61K9/32 A61K9/52 A61K9/54
D,A	EP-A-0 080 602 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) * page 2, line 1 - line 21 * * page 3, line 6 - line 13 * * page 17, line 10 - line 20 * * page 18, line 1 - line 20 * * page 20, line 14 - line 22 *	1-10	
A	GB-A-760 403 (ABBOT LABORATORIES) * page 1, line 11 - line 34 * * page 2, line 31 - line 70 * * page 6, line 3 - line 18 *	1-10	
A	DE-A-32 33 764 (R.P.SCHERER) * page 6, line 7 - page 7, paragraph 3 * * page 8, last paragraph - page 9, line 1 *	1-10	TECHNICAL FIELDS SEARCHED (Int.Cl.4) A61K
A	PATENT ABSTRACTS OF JAPAN vol. 8 no. 106 (C-223) [1543] ,18 May 1984 & JP-A-59 020219 (SHINETSU KAGAKU KOGYO K.K.) 1 February 1984, * abstract *	1-10	
E	EP-A-0 446 961 (TAKEDA CHEMICAL INDUSTRIES LTD.) * page 2 - page 3, line 6 * * page 7, line 50 - page 8, line 11 * * page 8, line 25 - line 32; claims 12,20-27; examples 7,9 *	1-10	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 April 1995	Muellners, W

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 20 1612

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.4)
E	EP-A-0 423 748 (TAKEDA CHEMICAL INDUSTRIES LTD.) * claims 11,19-31 * ---	1-10	
E	EP-A-0 237 200 (TAKEDA CHEMICAL INDUSTRIES LTD.) * claims 1,9,10 * -----	1-10	
			TECHNICAL FIELDS SEARCHED (Int.Cl.4)

The present search report has been drawn up for all claims

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X : particularly relevant if taken alone
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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(54) Vehicles for oral adminstration of pharmaceutically active acide labile substances

Vehikel für die orale Verarbreichung säurelabiler Pharmaka

Véhicules pour l'administration orale de substances pharmaceutiques sensibles aux acides

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(56) References cited:
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EP-A- 0 173 664
EP-A- 0 237 200
EP-A- 0 423 748
EP-A- 0 446 961
DE-A- 3 233 764
GB-A- 760 403

- **PATENT ABSTRACTS OF JAPAN vol. 8 no. 106 (C-223) [1543] ,18 May 1984 & JP-A-59 020219 (SHINETSU KAGAKU KOGYO K.K.) 1 February 1984,**

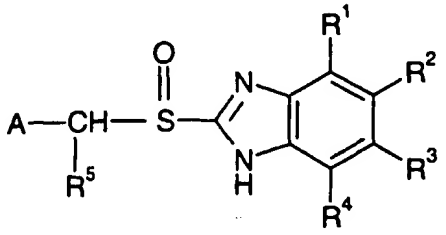
EP 0 565 210 B1

Description

[0001] The present invention is related to an improved administration vehicle for oral administration of acid labile substances.

[0002] Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

[0003] A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



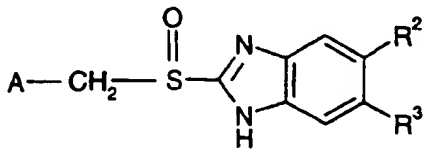
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4, are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

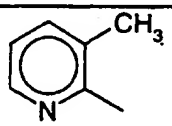
[0004] The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

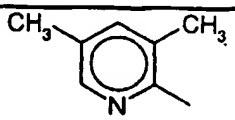
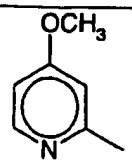
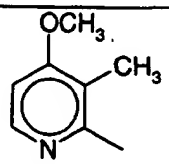
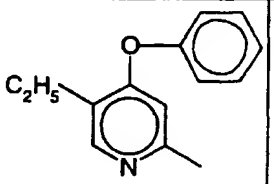
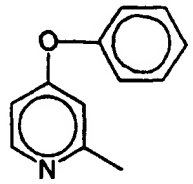
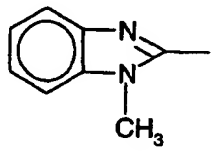
[0005] As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2-(2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g 2- (2-dimethylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brandstrom and H. Larsson "Evidence for acid-induced transformation of omeprazole into active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

[0006] The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes for the translation to the active moiety	
			at pH=2	at pH=7
1.		5-$COOOCH_3$; 6-CH_3	11	150

Compound No	A	R^2 R^3	Half-life (minutes for the translation to the active moiety	
			at pH=2	at pH=7
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

[0007] Substituted sulfoxides, such as, for instance, the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

[0008] It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidly decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

[0009] In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water of gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

[0010] In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

[0011] US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

[0012] DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivates. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

[0013] DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

[0014] WO 85/03436 describes a pharmaceutical preparation wherein cores containing active drugs mixed with, for instance, buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestine is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

[0015] EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

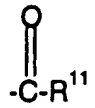
[0016] The object of the present invention is to provide an improved administration vehicle for oral administration of the pharmaceutically active acid labile compounds of the general formula I above wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3, and R^4, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

or halogen and R^5 is H or lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole; or the acide labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more

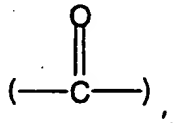
inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

R^1, R^2, R^3 and R^4, which are the same or different and especially

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) -CN
(d) -CHO
(e) $-CF_3$
(f)



(g) $-O-C-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(l) -alkylthio containing 1-6 carbon atoms
(m) $-NO_2$
(n) -akylsulfinyl containing 1-6 carbon atoms
(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 subsituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of theses substituents together form one or two oxo groups



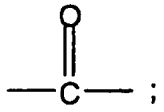
whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same of different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxyalkoxy containing 1-4 carbon atoms
(c) alkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is

(a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is —O— or



;

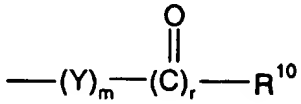
n is 0 or 1;

B is

(a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkynylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is

(a) H
(b) -CN O
(c) -C-R^9
(d)



wherein

R^9 is

(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;
r is 0 or 1;
Y is

(a) -O-
(b) -NH-
(c) -NR^{10}-;

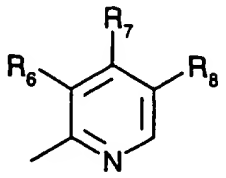
R^{10} is

(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or
(b) alkyl containing 1-6 carbon atoms;

R^7 is

(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(f) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms
(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or
(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$

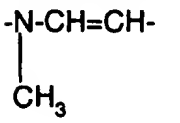
$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$

$-O-CH=CH-$

$-NH-CH=CH-$



wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

[0017] The object of the present invention is thus to provide an improved administration vehicle for an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole as claimed in claim 1. Another compound, which may be enteric coated according to the invention is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole. The administration vehicle makes the formulation stable to discolouration and resistant to dissolution in acid media. It dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The formulation is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

[0018] As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

[0019] The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

[0020] From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

[0021] The acid labile compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less that pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $Al_2O_3 . 6MgO . CO_2 . 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 . 4H_2O)$, $MgO . Al_2O_3 . 2SiO_2 . nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting salt of the active compound

such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

[0022] The powder mixture is then formulated into small beads i.e. pellets, or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

[0023] The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3 \cdot 6MgO \cdot CO_2 12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O)$, $MgO \cdot Al_2O_3 \cdot 2SiO_2 \cdot nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering compounds such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

[0024] The separating layer consists of one or more water soluble inert layer, optionally containing pH-buffering compounds.

[0025] The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance, sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

[0026] In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet a layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers colorants, pigments, titanium dioxide, talc and other additives may also be included into the separating layer.

[0027] The enteric layer coating layer is applied on to the subcoated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions or polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit ® L 12,5 or Eudragit ®L 100 (Rohm Pharma), or similar compounds used to obtain enteric coatings.

[0028] The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric® (FMC Corporation), Eudragit® L100-55 (Rohm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex® (Pfizer), phthalic acid esters, dibutyl succinate or similar plasticizers.

[0029] The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20% of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

[0030] Thus, the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance, the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

[0031] The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

[0032] A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

[0033] The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the novel oral dosage form represents a further aspect of the invention.

[0034] The invention is described in detail in the following examples:

EXAMPLES

[0035] Examples 1-3 exemplify the invention.

Example 1

Uncoated pellets

[0036]

I	Lactose powder	253 g
	Lactose anhydrous	167 g
	Hydroxypropyl cellulose	25 g
II	Compound 1, Table 1	50 g
	Sodium lauryl sulphate	5 g
	Disodium hydrogen phosphate	1.5g
	Sodium dihydrogen phosphate	0.1g
	Distilled water	125 g

[0037] The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

[0038]

III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

[0039] The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

[0040]

IV	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

[0041] The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

[0042] Formulation with the sodium salt of compound 2 according to Table 1.

Uncoated pellets

[0043]

I	Compound 2, Table 1 sodium salt	339 g
	Mannitol powder	2 422 g
	Lactose anhydrous	120 g
	Hydroxypropyl cellulose	90 g
	Microcrystalline cellulose	60 g
II	Sodium lauryl sulphate	7 g
	Distilled water	650 g

[0044] The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture 1.

Subcoated pellets

[0045]

III	Uncoated pellets	500 g
	Hydroxypropyl methylcellulose	20 g
	Aluminium hydroxide/magnesium carbonate	4 g
	Distilled water	400 g
IV	Pellets subcoated with III	500 g
	Hydroxypropyl methylcellulose	20 g
	Distilled water	400 g

[0046] The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

[0047]

V	Subcoated pellets	500 g
	Hydroxypropyl methylcellulose phthalate	57 g
	Cetyl alcohol	3 g
	Acetone	540 g
	Ethanol	231 g

[0048] The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

[0049] Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

[0050]

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg

(continued)

TOTAL	160 mg

[0051] Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

[0052]

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [$Al_2O_3 \cdot 6MgO \cdot CO_2 \cdot 12H_2O$]	0.3 mg

Separating layer (outer)

[0053]

Hydroxypropyl cellulose	2 mg

[0054] The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

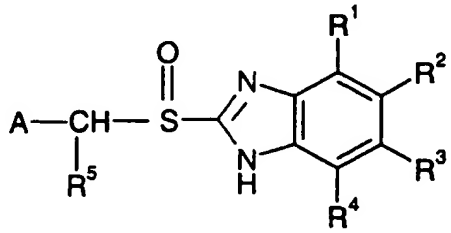
[0055]

Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

[0056] The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

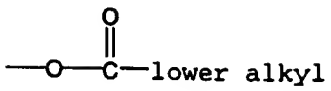
Claims

1. Improved administration vehicle for oral administration of pharmaceutically active acid labile substances, prone to discolouration, of the general formula I



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,



or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5. dimethyl-2-pyridinyl) methyl]-sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylamino-benzyl)-sulfinyl]-benzimidazole as the active ingredient comprising:

i) a core containing the pharmaceutically active acid labile substance,
ii) a subcoating applied on said core and
iii) an enteric coating applied on said subcoating, characterized in that:
iv) the subcoating part of the vehicle is made out of one or more inert reacting layers, comprising tablet excipients,
v) the excipients are soluble or rapidly disintegrating in water, or polymeric water soluble filmformig compounds, optionally containing pH-buffering alkaline compounds,
vi) the core part of the vehicle contains an active substance as defined in the general formula I, as the pharmaceutically active acid labile substance to be administered together with the alkaline substance,
vii) the alkaline substance in vi) is an alkaline reacting compound or an alkline salt of the active substance according to general formula I, optionally mixed with an alkaline reacting compound, and
viii) the vehicle adopts the form of a number of small beads optionally forming a tablet or a tablet as such.

2. Improved administration vehicle according to claim 1, wherein the subcoating of the core containing the active substance comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

3. Improved administration vehicle according to claim 1 wherein the applied subcoating comprises two or more sublayers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO.\ CO_2.12H_2O$ or $MgO.Al_2O_3.\ 2SiO_2.nH_2O$, wherein n not is an integer and less than two.

4. Improved administration vehicle according to claim 1, wherein the alkaline core comprising the acid labile compound contains a pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

5. Improved administration vehicle according to claim 4 wherein the alkaline compound which the acid labile compound is mixed with comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

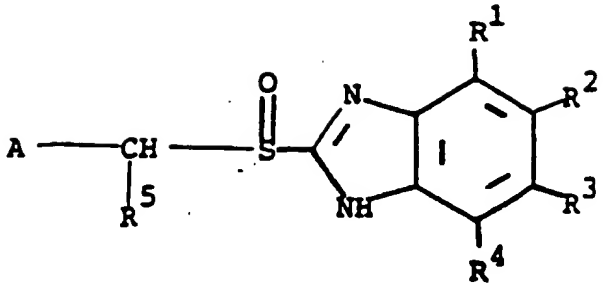
6. Improved administration vehicle according to claim 1, wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. Improved administration vehicle according to claim 6 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an otherwise alkaline compound.

8. Improved administration vehicle according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. Improved administration vehicle according to claim 1 wherein the dosage form containing the administration vehicle with the acid labile compound has a water content which does not exceed 1.5% by weight.

10. Process for the preparation of vehicles for oral administration of pharmaceutically active acid labile substances, stable to discolouration of the general formula



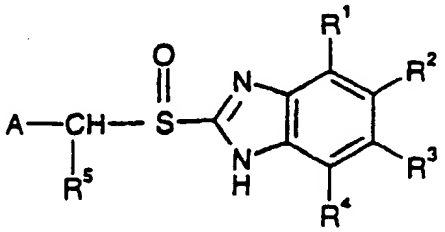
I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,

or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethyl-aminobenzyl)sulfinyl]-benzimidazole as the active ingredient characterized in that the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, either in the form of a number of small beads optionally forming a tablet, or a tablet as such are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

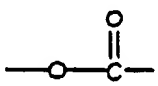
Patentansprüche

1. Verbessertes Verabreichungsvehikel zur oralen Verabreichung von säurelabilen pharmazeutischen Wirkstoffen, die sich leicht verfärben, mit der allgemeinen Formel I



I

in welcher A eine gegebenenfalls substituierte heterocyclische Gruppe darstellt, R^1, R^2, R^3 und R^4 gleich oder verschieden sind und jeweils vorzugsweise Wasserstoff, niederes Alkyl, niederes Alkoxy, $-CF_3$,



niederes Alkyl oder Halogen darstellen und R^5 H oder eine niedere Alkylgruppe darstellt, wobei "niedere" 1-6 Koh-

lenstoffatome bedeutet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazol; oder die säurelabile Verbindung ist 2-1(2-Dimethylamino-benzyl)-sulfinyl]-benzimidazol als Wirkstoff, gekennzeichnet durch

i) einen Kern, der den saurelabilen pharmazeutischen Wirkstoff enthält,
ii) eine untere Beschichtung, die auf den Kern aufgetragen ist, und
iii) einen enterischen Bezug, der auf die untere Beschichtung aufgetragen ist, dadurch gekennzeichnet, daß
iv) die untere Beschichtung des Vehikels aus einer oder mehreren inerten reagierenden Schichten besteht, die Tablettenträgerstoffe enthalten,
v) die Trägerstoffe wasserlöslich sind bzw. schnell in Wasser zerfallen, oder polymere wasserlösliche filmbildende Verbindungen sind, die gegebenenfalls pH-puffernde alkalische Verbindungen enthalten,
vi) der Kern des Vehikels einen durch die allgemeine Formel I definierten Wirkstoff als säurelabilen pharmazeutischen Wirkstoff enthält, der zusammen mit der alkalischen Substanz verabreicht werden soll,
vii) die alkalische Substanz in vi) eine alkalische reagierende Verbindung oder ein alkalisches Salz des Wirkstoffes gemäß der allgemeinen Formel I ist, die gegebenenfalls mit einer alkalisch reagierenden Verbindung gemischt vorliegt, und
viii) das Vehikel die Form einer Anzahl kleiner Perlen, die gegebenenfalls eine Tablette bilden, oder einer Tablette als solcher hat.

2. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß die untere Beschichtung des den Wirkstoff enthaltenden Kerns aus Hydroxypropylmethylcellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon besteht.

3. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß die aufgetragene untere Beschichtung aus zwei oder mehr Unterschichten besteht, wobei die innere Unterschicht eine oder mehrere der folgenden Verbindungen enthält: Magnesiumoxid, Magnesiumhydroxid oder den Verbundstoff $Al_2O_3.6MgO.CO_2.12H_2O$ oder $MgO.Al_2O_3.2SiO_2.nH_2O$, wobei n keine ganze Zahl und kleiner als zwei ist.

4. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß der alkalische Kern, der die säurelabile Verbindung beinhaltet, eine pH-puffernde alkalische Verbindung enthält, die der Mikroumgebung der säurelabilen Verbindung einen pH von 7-12 verleiht.

5. Verbessertes Verabreichungsvehikel gemäß Anspruch 4, dadurch gekennzeichnet, daß die alkalische Verbindung, mit der die säurelabile Verbindung gemischt ist, eine oder mehrere der folgenden Verbindungen enthält: Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, -phosphat oder -citrat, die Aluminium/Magnesium-Verbundstoffe $Al_2O_3.6MgO.CO_2.12H_2O$ oder $MgO.Al_2O_3.2SiO_2.nH_2O$, wobei n keine ganze Zahl und kleiner als zwei ist.

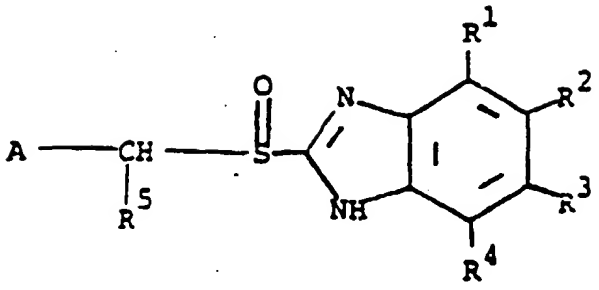
6. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß der alkalische Kern ein alkalisches Salz der säurelabilen Verbindung wie z. B. das Natrium-, Kalium-, Magnesium-, Calcium- oder Ammoniumsalz, enthält.

7. Verbessertes Verabreichungsvehikel gemäß Anspruch 6, dadurch gekennzeichnet, daß der alkalische Kern ein alkalisches Salz der säurelabilen Verbindung in einer Mischung mit einer ansonsten alkalischen Verbindung enthält.

8. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß der enterische Bezug Hydroxypropylmethylcellulosephthalat, Celluloseacetatphthalat, ein MethacrylsäureMethacrylsäuremethylester-Copolymerisat oder Polyvinylacetatphthalat und gegebenenfalls einen Weichmacher enthält.

9. Verbessertes Verabreichungsvehikel gemäß Anspruch 1, dadurch gekennzeichnet, daß die Darreichungsform, die das Verabreichungsvehikel mit der säurelabilen Verbindung enthält, einen Wassergehalt hat, der 1,5 Gewichtsprozent nicht überschreitet.

10. Verfahren zur Herstellung von Vehikeln zur oralen Verabreichung von säurelabilen pharmazeutischen Wirkstoffen, die sich nicht verfärben, der allgemeinen Formel



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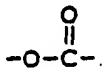
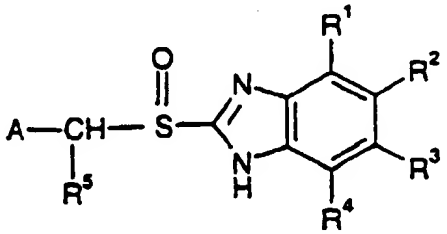


niederes Alkyl oder Halogen darstellen und R^5 H oder eine niedere Alkylgruppe darstellt, wobei "niedere" 1-6 Kohlenstoffatome bedeutet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazol; oder die säurelabile Verbindung ist 2-[(2-Dimethylamino-benzyl)-sulfinyl]-benzimidazol als Wirkstoff, dadurch gekennzeichnet, daß die saurelabile Verbindung, gemischt mit einer alkalisch reagierenden Verbindung, oder ein alkalisches Salz des Wirkstoffes, gegebenenfalls in einer Mischung mit alkalisch reagierenden Verbindungen, entweder in Form einer Anzahl kleiner Perlen, die gegebenenfalls eine Tablette bilden, oder einer Tablette als solcher, mit einem oder mehreren inerten unterbeschichtenden Schichten, die Tablettenträgerstoffen enthalten, die wasserlöslich sind bzw. schnell in Wasser zerfallen, oder polymere wasserlösliche filmbildende Verbindungen sind, die gegebenenfalls pH-puffernde alkalische Verbindungen enthalten, zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht, bei der es sich um einen enterischen Bezug handelt, beschichtet wird, woraufhin die mit einer unteren Schicht versehenen Kerne weiter mit dem besagten äußeren enterischen Bezug beschichtet werden.

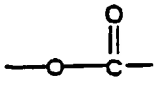
Revendications

1. Véhicule d'administration amélioré pour l'administration orale de substances pharmaceutiquement actives, sensibles aux acides et dont la couleur est susceptible d'être altérée, de formule générale I



I

dans laquelle A est un groupe hétérocyclique éventuellement substitué, R^1, R^2, R^3 et R^4 sont identiques ou différents et de préférence un hydrogène, un alkyle inférieur, un alcoxy inférieur, $-CF_3$,



alkyle inférieur ou un halogène et R^5 est H ou un groupe alkyle inférieur, où "inférieur" signifie 1-6 atomes de carbone, excepté le composé omeprazole, le 5-méthoxy-2-1[(4-méthoxy-3,5-diméthyl-2-pyridinyl)-méthyl]sulfinyl]-1H-benzimidazole ; ou le composé sensible aux acides est le 2-1(2-diméthyl-aminobenzyl)sulfinyl]benzimidazole en tant qu'ingrédient actif, comprenant :

i) un coeur contenant la substance pharmaceutiquement active, sensible aux acides,
ii) un sous-enrobage appliqué sur ledit coeur, et
iii) un enrobage entérique, appliqué sur ledit sousenrobage, caractérisé en ce que :
iv) la partie sous-enrobage du véhicule est constituée d'une ou de plusieurs couches réagissant de manière inerte, comprenant des excipients de comprimé,
v) les excipients sont solubles ou se désagrègent rapidement dans l'eau, ou des composés polymères hydrosolubles filmogènes, contenant éventuellement des composés alcalins tampons,
vi) la partie coeur du véhicule contient une substance active telle que définie dans la formule générale I, en tant que substance pharmaceutiquement active, sensible aux acides, destinée à être administrée conjointement avec la substance alcaline,
vii) la substance alcaline dans vi) est un composé réagissant de manière alcaline ou un sel alcalin de la substance active selon la formule générale I, éventuellement mélangé avec un composé réagissant de manière alcaline, et
viii) le véhicule adopte la forme d'un certain nombre de petites billes formant éventuellement un comprimé, ou d'un comprimé en tant que tel.

2. Véhicule d'administration amélioré selon la revendication 1, dans lequel le sous-enrobage du coeur contenant la substance active comprend de l'hydroxypropylméthylcellulose, de l'hydroxypropylcellulose ou de la polyvinylpyrrolidone.

3. Véhicule d'administration amélioré selon la revendication 1, dans lequel le sous-enrobage appliqué comprend deux sous-couches ou plus et où la sous-couche interne contient l'un ou plusieurs parmi l'oxyde de magnésium, l'hydroxyde de magnésium ou la substance composite $Al_2O_3.6MgO.CO_2.12H_2O$ ou $MgO.Al_2O_3.2SiO_2.nH_2O$, où n n'est pas un entier et est inférieur à deux.

4. Véhicule d'administration amélioré selon la revendication 1, dans lequel le coeur alcalin comprenant le composé sensible aux acides contient un composé alcalin tampon conférant un pH de 7-12 au micro-environnement du composé sensible aux acides.

5. Véhicule d'administration amélioré selon la revendication 4, dans lequel le composé alcalin avec lequel est mélangé le composé sensible aux acides, comprend l'un ou plusieurs parmi l'oxyde, l'hydroxyde ou le carbonate de magnésium, l'hydroxyde d'aluminium, le carbonate, le phosphate ou le citrate d'aluminium, de calcium, de sodium ou de potassium, les composés composites à l'aluminium/magnésium $Al_2O_3.6MgO.CO_2.12H_2O$ ou $MgO.Al_2O_3.2SiO_2.nH_2O$, où n n'est pas un entier et est inférieur à deux.

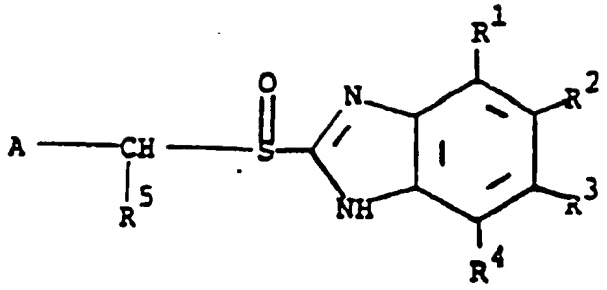
6. Véhicule d'administration amélioré selon la revendication 1, dans lequel le coeur alcalin comprend un sel alcalin du composé sensible aux acides, tels que le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium.

7. Véhicule d'administration amélioré selon la revendication 6, dans lequel le coeur alcalin comprend un sel alcalin du composé sensible aux acides mélangé avec un composé autrement alcalin.

8. Véhicule d'administration amélioré selon la revendication 1, dans lequel l'enrobage entérique comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate-phtalate de cellulose, de l'acide méthacrylique/ester méthylique d'acide méthacrylique copolymérisé ou de l'acétate-phtalate de polyvinyle, contenant éventuellement un plastifiant.

9. Véhicule d'administration amélioré selon la revendication 1, dans lequel la forme de dosage contenant le véhicule d'administration avec le composé sensible aux acides présente une teneur en eau qui ne dépasse pas 1,5% en poids.

10. Procédé de préparation de véhicules pour l'administration orale de substances pharmaceutiquement actives, sensibles aux acides et stables vis-à-vis d'une altération de la couleur, de formule générale



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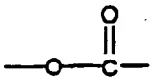

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